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# Transvenous electrical cardioversion of atrial fibrillation in horses: Horse and procedural factors correlated with success and recurrence

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## Abstract

**Background:** Transvenous electrical cardioversion (TVEC) is 1 of the main treatment options for atrial fibrillation (AF) in horses. Large-scale studies on factors affecting success and prognosis have primarily been performed in Standardbred populations.

**Hypothesis/Objectives:** To determine factors affecting cardioversion success, cardioversion difficulty and recurrence in a predominant Warmblood study sample.

**Animals:** TVEC records of 199 horses.

**Methods:** Retrospective study of TVEC procedures of horses admitted for AF without severe echocardiographic abnormalities. Horse and procedural factors for success and cumulative amount of energy (≤ 600 J vs > 600 J) were determined using multivariable logistic regression. A survival analysis was performed to determine risk factors for recurrence.

**Results:** Two hundred and thirty-one TVEC procedures were included, with a 94.4% success rate and 31.9% recurrence rate (51/160). Mitral regurgitation (OR 0.151, 95% CI 0.032-0.715, $P = .02$) and AF cycle length (OR 1.05, 95% CI 1.01-1.09, $P = .02$) were independent determinants for success. Catheter type (OR 0.154, 95% CI 0.074-0.322, $P < .001$), previous AF episode (OR 3.10, 95% CI 1.20-8.01, $P = .02$), tricuspid regurgitation (OR 2.54, 95% CI 1.25-5.13, $P = .01$), and body weight (OR 1.009, 95% CI 1.003-1.015, $P = .004$) were significantly correlated with cumulative amount of energy delivered. Significant risk factors for recurrence after a first AF episode were sex (stallion; HR 3.05, 95% CI 1.34-6.95, $P = .008$), mitral regurgitation (HR 1.91, 95% CI 1.08-3.38, $P = .03$), and AF duration (HR 1.001, 95% CI 1.0001-1.0026, $P = .04$).

**Conclusions and Clinical Importance:** Both horse and procedural factors should be considered when assessing treatment options and prognosis in horses with AF.

**Abbreviations:** AF, atrial fibrillation; AFCL, atrial fibrillation cycle length; APD, atrial premature depolarization; ERAF, early recurrence of atrial fibrillation; HR, hazard ratio; IRAF, immediate recurrence of atrial fibrillation; J, joules; LA, left atrium; MR, mitral regurgitation; OR, odds ratio; PA, pulmonary artery; RA, right atrium; R-AFCL, atrial fibrillation cycle length measured in the right atrium; TR, tricuspid regurgitation; TVEC, transvenous electrical cardioversion; VIF, variance inflation factor.

Annelies Decloedt and Gunther van Loon are regarded as joint senior authors.

KEYWORDS
amiodarone, arrhythmia, cardiology, equine, sotalol

## 1 | INTRODUCTION

Atrial fibrillation (AF) is the most common abnormal arrhythmia affecting performance in horses and has an estimated prevalence of 2.5%.[1,2] In contrast with human medicine,[3] rhythm control, rather than rate control, is pursued in horses, as it is often important that horses can return to their previous performance level without further compromising the safety of rider or driver.[1] Treatment methods can be divided in pharmacological cardioversion, primarily using quinidine sulfate,[4] and transvenous electrical cardioversion (TVEC).[5,6] Both methods have high success rates, up to 91%[4,7-9] and 99%[5,10,11] respectively, depending on the studied sample. In contrast with pharmacological cardioversion, TVEC requires specialized equipment, accommodation, and personnel as it is a highly technical procedure.[12-15] Moreover it involves general anesthesia which carries a risk for perioperative death (0.9%).[16] On the other hand the adverse effects caused by administration of antiarrhythmic drugs, which can occur in up to 75% of cardioversions with quinidine sulfate,[17] can be avoided.[12]

Factors influencing success rate and recurrence rate of TVEC, both horse- and procedure-related, have primarily been reported in Standardbred populations.[5,13] In Warmblood horses, typically used in less intensive sport disciplines, AF will generally cause more subtle clinical signs, resulting in delayed diagnosis and more long-standing AF. This causes more atrial remodeling and therefore presumably a more difficult conversion.[17,18] The goal of this retrospective study is to describe horse and TVEC characteristics and report the horse and procedural factors influencing the success and recurrence rate of TVEC in a clinical study sample mainly consisting of Warmbloods. The principal hypothesis in this study was that success rate is influenced by height at the withers, body weight, AF duration, breed, sex, age, previous AF episode, previous unsuccessful cardioversion attempt, AF cycle length, echocardiographic abnormalities, year of conversion, sotalol premedication, catheter type, depth of catheter insertion, and impedance. As the success rate in our study was high, we also evaluated the influence of these factors on cumulative amount of energy applied during the TVEC as a measure of difficulty of cardioversion. Our secondary hypothesis was that AF recurrence rate is influenced by the same factors as in our primary hypothesis (except for catheter type, insertion depth, and impedance) and in addition number of shocks, energy requirement, immediate recurrence of AF (IRAF), administration of amiodarone in refractory cases, and follow-up treatment with sotalol. In addition, it was hypothesized that there would be a correlation between the need for pacing and the cumulative amount of energy administered, between catheter insertion depth and body weight and height at the withers, and between AF cycle length and AF duration. Also, it was hypothesized that there would be a significant difference between the 2 types of catheters regarding impedance and cumulative amount of energy administered until conversion.

## 2 | MATERIALS AND METHODS

### 2.1 | Study sample

All medical records of TVECs between 2008 and 2019 treated by the Equine Cardioteam, Department of Large Animal Internal Medicine, Ghent University, were reviewed. Cases for which treatment was discouraged due to a high recurrence risk (global assessment based on case history and severe echocardiographic abnormalities such as severe chamber dilation or severe valvular regurgitation), but were nevertheless treated, were excluded from the study. In each case, a standard echocardiographic examination had been performed. Presence of chamber dilation was based on a combination of standard chamber dimensions[19-22] and overall subjective assessment. Presence and grade of valvular regurgitation was assessed based on the size and duration of the regurgitant jet and dilation of the receiving chamber.[20,23,24] Trivial regurgitations were regarded as not clinically relevant and therefore recorded as "no regurgitation." Details on the quantitative component of the echocardiographic assessment are provided in Data S1. For each procedure, the following horse characteristics were recorded: age (years), sex (mare, stallion, gelding), body weight (kg), height at the withers (cm), breed (Warmblood, Trotter, Thoroughbred, Friesian, Quarter Horse, Arabian Horse), sport discipline, estimated AF duration, previous AF episode, previous unsuccessful cardioversion attempt, echocardiographic findings, AF cycle length measured intracardially in the right atrium (R-AFCL; ms), AF recurrence (0/1), and time to recurrence (days). Duration of AF was estimated based on the history; if AF was detected coincidently or no information about AF duration was available, the AF duration was inserted as a missing value. The R-AFCL was measured without sedation as described previously.[25] In horses in which the R-AFCL without sedation was not available, the R-AFCL with sedation was included, as the difference between the 2 is small and clinically irrelevant.[26] Follow-up regarding AF recurrence was based on confirmation of normal heart auscultation through follow-up visits and email and telephone correspondence with the owner or referring veterinarian.

### 2.2 | Transvenous electrical cardioversion

TVEC was performed as described (Lifepak 20, Medtronic Physio-Control, Maastricht, The Netherlands).[6,18] A first biphasic shock was delivered at 150 J, and if sinus rhythm was not achieved, additional shocks were administered at 200, 250, 300, and 360 J with every subsequent shock at 360 J until conversion or decision to stop the procedure. Sixty IU/kg body weight of heparin (Heparine Leo, Leo Pharma N.V./S.A., Lier, Belgium) was administered intravenously at the start of the procedure. Two types of shock catheters have been used: a custom open-lumen 9.5 cm coil catheter[14] (Rhythm Technologies, Huntington, CA; "Type A") between 2008 and 2013, and a 12 cm coil catheter (Gaeltec Devices Ltd, Isle of Skye, UK; "Type B") between 2013 and 2019, without overlap of the 2 types. Catheter positioning was guided using echocardiography. Depth of catheter insertion was determined at the end of the procedure (successful cardioversion or decision to stop the procedure), based upon the length of the noninserted part of the catheter. The following procedural characteristics were recorded: success/failure, year, number of shocks, amount of energy for cardioversion (Joules, J), cumulative amount of energy (Joules, J), impedance of the converting shock (Ohm, Ω), catheter type (Type A, Type B), depth of catheter insertion (cm), need for pacing, IRAF, periprocedural administration of medication and early recurrence of AF (ERAF). If recurrence occurred before recovery it was defined as IRAF, while ERAF was defined as recurrence of AF after recovery and within 3 days after TVEC, since electrical reverse remodeling is completed at the earliest at this time point.[27-29] In case of IRAF, another cardioversion was attempted during the same anesthesia until stable sinus rhythm was achieved or decision to stop the procedure. Only the first cardioversion was taken into account for the cumulative amount of energy.

## 2.3 | Data analysis

Normality of the distribution of the variables was determined by inspection of the Q-Q plots. Normally distributed data are presented as mean ± SD and nonnormally distributed data as median (range). Missing data were imputed using multiple imputation with use of predictive-mean matching for continuous variables.[30] Fifty imputed datasets were created, each based on 15 cycles of imputation. Final analysis was performed on the pooled data of the 50 imputed datasets. Outcome variables (ie, cumulative amount of energy and recurrence) were not imputed. The predictors of success and difficulty of cardioversion were studied using multivariable logistic regression. Difficulty of cardioversion was represented by the cumulative amount of energy administered until conversion, with a cumulative amount of energy of ≤ 600 J regarded as "easy" and > 600 J as "difficult." This cutoff was chosen based on clinical experience, in order to discern easy from challenging procedures. This approach was preferred rather than treating this outcome variable as a continuous variable since this variable has only a selection of possible outcomes which are not at regular intervals. First, a univariable analysis was performed for each possible predictor: height at the withers, body weight, breed, sex, age, AF duration, previous AF episode, previous unsuccessful cardioversion attempt, R-AFCL, presence of chamber dilation, presence of valvular regurgitation, valvular regurgitation grade ("none," "mild," "moderate"), sotalol premedication, year of conversion, catheter type, depth of the right atrial (RA) catheter, depth of the pulmonary artery (PA) catheter and impedance. For each variable, the odds ratio (OR) with 95% confidence interval (95% CI) and *P*-value was calculated and variables with $P < .2$ were withheld for multivariable analysis. The variance inflation factor (VIF) and Eigenvalues were inspected to assess collinearity, and if present, the variable with the lowest *P*-value was withheld for further analysis. Multivariable logistic regression was performed using backward stepwise approach. Model fit was assessed using the Hosmer-Lemeshow test and by determining the Nagelkerke $R^2$ and Cook's distance.

A survival analysis was performed to determine risk factors for recurrence between 3 days and 1 year after cardioversion by building a Cox proportional hazards model. Horses with a follow-up of less than 1 year were right-censored at the time-point of last follow-up. Horses with ERAF were excluded as recurrence occurred within 3 days in these cases. IRAF was not regarded as recurrence, as this happens before recovery and either results in restoration of sinus rhythm or failure of the TVEC procedure. Two separate analyses were performed: 1 including the cases which were treated for their first AF episode and a second including the cases treated for their last AF episode, the latter in order to assess the effect of a previous AF episode. All possible risk factors were first analyzed univariably: height at the withers, body weight, breed, sex, age, AF duration, previous AF episode, previous unsuccessful cardioversion attempt, R-AFCL, presence of chamber dilation, presence of valvular regurgitation, valvular regurgitation grade ("none," "mild," "moderate"), sotalol premedication, number of shocks, amount of energy at conversion, cumulative amount of energy, IRAF, administration of amiodarone in refractory cases and follow-up treatment with sotalol. For each variable the hazard ratio (HR), 95% CI and *P*-value was calculated, and variables with a *P*-value $< .2$ were selected for inclusion in the multivariable analysis. Collinearity was assessed using the VIF and Eigenvalues and if present only the most significant variable was selected for further analysis. Backward stepwise regression was applied to determine the risk factors for recurrence. The proportional hazard assumption was tested by including interaction terms between the variables and time and by inspecting the Schoenfeld residuals. Model fit was assessed by inspecting the Martingale and deviance residuals. Kaplan-Meier survival curves were constructed to illustrate the relation between some categorical variables and recurrence, for which time of follow-up was set as time variable and AF recurrence as outcome variable.

The relation between need for pacing and cumulative amount of energy was evaluated using a Mann-Whitney-*U* test. Pearson correlation coefficients were calculated for the correlation between depth of the different catheter insertions and body weight or height at the withers. The Spearman correlation coefficient was calculated to assess the relation between R-AFCL and estimated AF duration. In order to distinguish the influence of catheter type and year in which the TVEC was performed, a Mann Whitney-*U* test was performed on a limited sample of 52 TVEC procedures performed around the moment of catheter change to evaluate if there was a difference of cumulative amount of energy between the 2 catheter types. In addition, a Student's *t*-test was performed to assess the difference in impedance

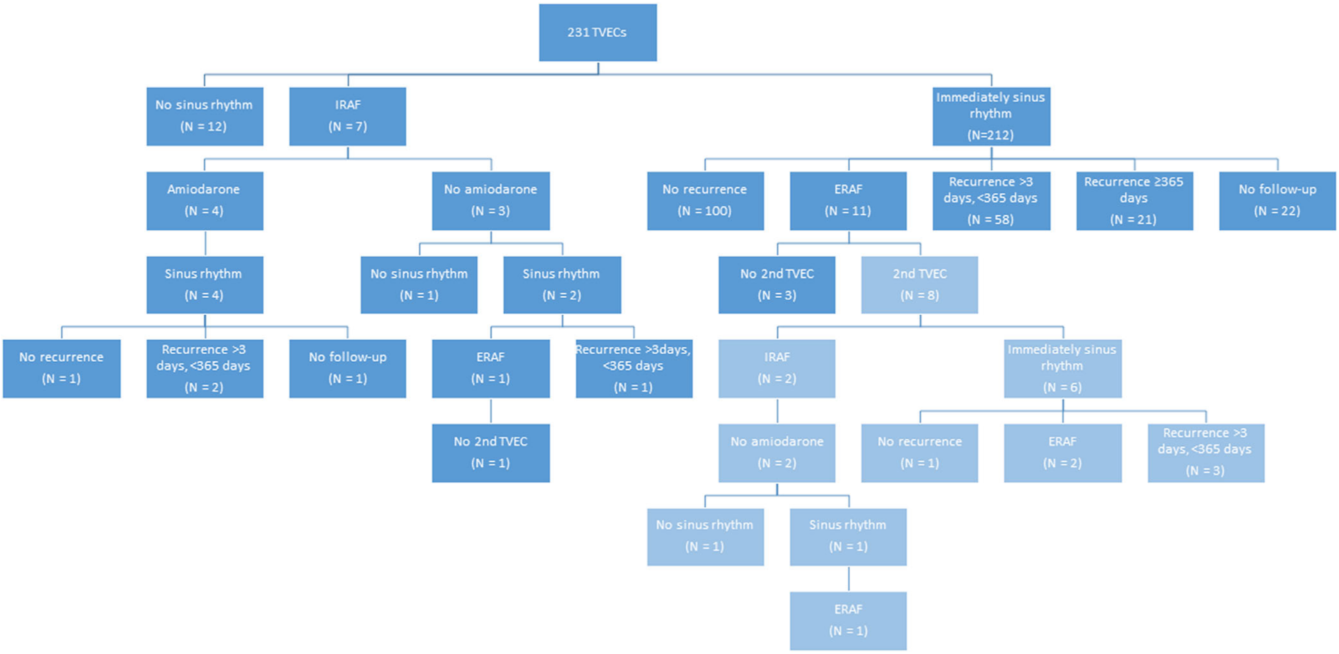


**FIGURE 1** Overview of all TVEC procedures and their outcome. The box in light blue represents TVECs included in the initial 231 TVECs. ERAF, early recurrence of atrial fibrillation; IRAF, immediate recurrence of atrial fibrillation; TVEC, transvenous electrical cardioversion

between catheter types on a sample of 16 TVEC procedures around the time of change of catheters.

All analyses were performed at a significance level of $P < .05$ using dedicated software (SPSS Statistics 25, IBM, Brussels, Belgium).

## 3 | RESULTS

The study sample consisted of 231 TVEC procedures performed on 199 horses: 166 Warmbloods, 27 Trotters, 2 Thoroughbreds, 2 Quarter Horses, 1 Friesian, and 1 Arabian Horse; 62 mares, 24 stallions, and 113 geldings; age 9 ± 4 years; body weight 578 ± 63 kg; height at the withers 171 ± 7 cm. Horses were used for show jumping (42.2%), dressage (17.6%), harness racing (13.6%), recreation (8.0%), eventing (5.0%), and others (3.5%; 10.1% discipline unknown). Of the 231 procedures, 199 cases were treated for their first episode of AF, 24 for their second, and 8 for their third. A previous unsuccessful cardioversion attempt had been performed in 21 cases (19 pharmacological cardioversions, 2 TVECs). AF duration could be estimated in 68.8% of the cases (60 days [1-1095 days]). Atrial fibrillation cycle length measured in the RA was 165 ± 20 ms (19 missing values). Type A catheters were used in the first 61 cases, Type B catheters in the following 170 cases. Temporary ventricular pacing after shock delivery was necessary in 15 cases. In 7 cases IRAF occurred. Left atrial dilation was present in 31 cases, left ventricular dilation in 5 cases, RA dilation in 5 cases, right ventricular dilation in 7 cases, and a combination of 2 or more chamber dilations in 49 cases. Regarding mild or moderate valvular regurgitation, mitral regurgitation (MR) was present in 40 cases, tricuspid regurgitation (TR) in 29 cases, aortic regurgitation in 11 cases, pulmonary regurgitation in 5 cases, and a combination of 2 or more regurgitations in 90 cases. Premedication included sotalol (2 mg/kg PO q12h for 3 days; 44 cases), amiodarone (6.52 mg/kg IV over 1 hour, followed by 1.1 mg/kg/h for 23 hours; 9 cases) and propafenone (2 mg/kg PO q8h for 3 days; 1 case). Amiodarone was administered during TVEC as continuation of premedication in 1 case with a history of ERAF and as a continuous rate infusion (5 mg/kg IV over 30 minutes) in 14 cases of refractory AF and 4 cases of IRAF. Post-TVEC medication included sotalol (2-3 mg/kg PO q12h for 4 weeks; 105 cases), amiodarone (IV for 15 minutes—36 hours; 11 cases), propafenone (2 mg/kg PO q8h for 4 weeks; 3 cases), quinidine sulfate (6 mg/kg IV, followed by 2.6 mg/kg/h IV for 18 hours; 1 case), quinapril (0.25 mg/kg PO q24h or q12h for 4 weeks; 6 cases), enalapril (0.25 mg/kg PO q12h for 2 months; 2 cases), and prednisolone (1 mg/kg PO for 4 weeks, while halving the dose gradually; 2 cases). Sinus rhythm was achieved in 218 procedures (94.4%), with a median number of 2 shocks (1–17), median energy of 200 J (150-360), median cumulative amount of energy of 350 J (150-5580), and mean impedance of 33 ± 8 Ω (12 missing values). The RA catheter was positioned at 77 ± 7 cm depth (26 missing values) and the PA catheter at 131 ± 5 cm depth (22 missing values). In 9 of 14 refractory cases, sinus rhythm was achieved after amiodarone administration. Repeated IRAF could be prevented in 4 cases by administration of amiodarone and sustained sinus rhythm was achieved. Of those 4 horses, 2 horses had recurrence within 1 year (at 27 and 270 days), 1 remained in sinus rhythm (follow-up of 406 days), and 1 was lost to follow-up (last known in sinus rhythm on day 132 post-TVEC). In 12 cases, ERAF occurred (Figure 1). Of these horses, 4 continued to be used for light work, 3 were retired, 2 converted with a second TVEC combined with amiodarone premedication, 2 converted with quinidine sulfate, 1 died during amiodarone pre-treatment for a second TVEC, and 1 was euthanized. Follow-up at least 1 year after successful cardioversion of a first AF episode (excluding the

**TABLE 1** Summary statistics of the study sample (231 TVECs)

| | Easy conversion (≤ 600 J cumulative amount of energy) | Difficult conversion (> 600 J cumulative amount of energy) | Unsuccessful |
|---|---|---|---|
| Number of cases | 162 (70.1%) | 56 (24.2%) | 13 (5.6%) |
| Breed | 130 Warmbloods<br>26 Trotters<br>2 Thoroughbreds<br>2 Quarter Horses<br>1 Friesian<br>1 Arabian Horse | 51 Warmbloods<br>5 Trotters | 13 Warmbloods |
| Sex | 43 mares<br>23 stallions<br>96 geldings | 26 mares<br>6 stallions<br>24 geldings | 3 mares<br>1 stallion<br>9 geldings |
| Age | 9 ± 4 years | 9 ± 4 years | 10 ± 3 years |
| Body weight | 569 ± 59 kg | 598 ± 62 kg | 610 ± 46 kg |
| Height at the withers | 170 ± 7 cm | 172 ± 6 cm | 174 ± 6 cm |
| Catheter type | 25 Type A<br>137 Type B | 29 Type A<br>27 Type B | 7 Type A<br>6 Type B |
| Number of shocks | 1 (1-3) | 5 (3-17) | 12 (1[a]-17) |
| Cumulative amount of energy administered | 150 (150-600) J | 1200 (750-5580) J | 3780 (150[a]-5580) J |
| Impedance | 31 ± 7 Ω | 37 ± 10 Ω | 28 ± 6 Ω |
| RA catheter depth | 77 ± 6 cm | 78 ± 9 cm | 76 ± 3 cm |
| PA catheter depth | 132 ± 5 cm | 129 ± 7 cm | 127 ± 9 cm |
| Previous AF | 16 | 13 | 3 |
| AF recurrence | 93 no<br>45 yes<br>24 unknown | 29 no<br>16 yes<br>11 unknown | NA |

Abbreviations: AF, atrial fibrillation; IRAF, immediate recurrence of atrial fibrillation; NA, not applicable; PA, pulmonary artery; RA, right atrium; TVEC, transvenous electrical cardioversion.

[a]TVEC procedure with sinus rhythm after 1 shock, but IRAF occurred. After multiple attempts and multiple IRAFs the procedure was aborted.

**TABLE 2** Variables included in the multivariable analysis for TVEC success, based on 231 TVEC procedures

| Variables | Level | N (including imputed values) | N (excluding missing data values) | OR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|
| Height at the withers | | 231 | 231 | 0.93 | 0.85-1.02 | .14 |
| Body weight | | 231 | 220 | 0.99 | 0.98-1.00 | .05 |
| R-AFCL | | 231 | 212 | 1.04 | 1.01-1.08 | .02 |
| LA dilation | No | 175 | 175 | Reference | | |
| | Yes | 56 | 56 | 0.347 | 0.112-1.08 | .07 |
| MR | No | 117 | 117 | Reference | | |
| | Yes | 114 | 114 | 0.163 | 0.035-0.75 | .02 |
| MR grade | None | 117 | 117 | Reference | | |
| | Mild | 80 | 80 | 0.214 | 0.042-1.09 | .06 |
| | Moderate | 34 | 34 | 0.101 | 0.019-0.55 | .008 |
| Year of conversion | | 231 | 231 | 1.19 | 1.01-1.41 | .04 |
| Catheter type | Type A | 61 | 61 | Reference | | |
| | Type B | 170 | 170 | 3.54 | 1.14-11.0 | .03 |
| Depth of the PA catheter | | 231 | 203 | 1.12 | 1.01-1.25 | .04 |

Abbreviations: 95% CI, 95% confidence interval; LA, left atrium; MR, mitral regurgitation; N, number of TVEC procedures; OR, odds ratio; PA, pulmonary artery; R-AFCL, atrial fibrillation cycle length in the right atrium; TVEC, transvenous electrical cardioversion.

**TABLE 3** Variables included in the multivariable analysis for a high cumulative amount of energy administered (> 600 J), based on 218 successful TVEC procedures

| Variables | Level | N (including imputed values) | N (excluding missing data values) | OR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|
| Height at the withers | | 218 | 218 | 1.04 | 0.99-1.10 | .08 |
| Body weight | | 218 | 208 | 1.008 | 1.003-1.014 | .003 |
| Sex | Mare | 69 | 69 | Reference | | |
| | Stallion | 29 | 29 | 0.43 | 0.155-1.20 | .11 |
| | Gelding | 120 | 120 | 0.41 | 0.213-0.80 | .009 |
| Previous AF episode | None | 195 | 195 | Reference | | |
| | 1 or more | 23 | 23 | 2.76 | 1.23-6.18 | .01 |
| R-AFCL | | 218 | 200 | 0.981 | 0.965-0.998 | .02 |
| LA dilation | No | 168 | 168 | Reference | | |
| | Yes | 50 | 50 | 1.70 | 0.86-3.38 | .13 |
| RA dilation | No | 173 | 173 | Reference | | |
| | Yes | 45 | 45 | 1.61 | 0.79-3.28 | .19 |
| MR | No | 115 | 115 | Reference | | |
| | Yes | 103 | 103 | 1.55 | 0.84-2.86 | .16 |
| MR grade | None | 115 | 115 | Reference | | |
| | Mild | 74 | 74 | 1.84 | 0.96-3.53 | .07 |
| | Moderate | 29 | 29 | 0.94 | 0.345-2.56 | .9 |
| TR | No | 119 | 119 | Reference | | |
| | Yes | 99 | 99 | 2.09 | 1.13-3.87 | .02 |
| TR grade | None | 119 | 119 | Reference | | |
| | Mild | 70 | 70 | 1.56 | 0.78-3.12 | .21 |
| | Moderate | 29 | 29 | 3.90 | 1.65-9.2 | .002 |
| PR grade | None | 202 | 202 | Reference | | |
| | Mild | 12 | 12 | 0.249 | 0.031-1.98 | .19 |
| | Moderate | 4 | 4 | 0.914 | 0.093-9.0 | .94 |
| Sotalol premedication | No | 178 | 178 | Reference | | |
| | Yes | 40 | 40 | 0.191 | 0.056-0.647 | .008 |
| Year of conversion | | 218 | 218 | 0.79 | 0.72-0.88 | <.001 |
| Catheter type | Type A | 54 | 54 | Reference | | |
| | Type B | 164 | 164 | 0.170 | 0.086-0.334 | <.001 |
| Depth of the PA catheter | | 218 | 196 | 0.92 | 0.87-0.98 | .005 |
| Impedance | | 218 | 206 | 1.09 | 1.04-1.13 | <.001 |

Abbreviations: 95% CI, 95% confidence interval; AF, atrial fibrillation; LA, left atrium; MR, mitral regurgitation; N, number of TVEC procedures; OR, odds ratio; PA, pulmonary artery; PR, pulmonary regurgitation; RA, right atrium; R-AFCL, atrial fibrillation cycle length in the right atrium; TR, tricuspid regurgitation; TVEC, transvenous electrical cardioversion.

first AF episode ERAF cases, N = 8) was available for 160 cases and showed a recurrence rate of 31.9% (51 cases). Median time to recurrence was 99 days (7-364 days). Of these cases that were in sinus rhythm at 1 year post-TVEC, 92 remained recurrence-free at a median follow-up time of 727 days (365-3799), and 17 experienced recurrences at a median time to recurrence of 548 days (366-1954). Summary statistics are given in Table 1.

Variables that met the *P*-value threshold for inclusion in the multivariable analyses are presented in Tables 2-5. In the multivariable model for TVEC success, presence of MR (OR 0.151, 95% CI 0.032-0.715, *P* = .02) and R-AFCL (OR 1.05, 95% 1.01-1.09, *P* = .02) were significant independent predictors. Catheter type (OR 0.154, 95% CI 0.074-0.322, *P* < .001), previous AF episode (OR 3.10, 95% CI 1.20-8.01, *P* = .02), presence of TR (OR 2.54, 95% CI 1.25-5.13, *P* = .01), and body weight (OR 1.009, 95% CI 1.003-1.015, *P* = .004) were significant predictors in the multivariable model for cumulative amount of energy administered until conversion. In the multivariable proportional hazards model for recurrence within 1 year after a first AF episode (175 cases), being a stallion (HR 3.05, 95% CI 1.34-6.95, *P* = .008, Figure 2), presence of MR (HR 1.91, 95% CI 1.08-3.38, *P* = .03), and estimated AF duration

**TABLE 4** Variables included for the multivariable analysis of AF recurrence within 1 year, based on 175 horses with a first AF episode

| Variables | Level | N (including imputed missing values) | N (excluding missing data values) | HR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|
| Body weight | | 175 | 175 | 0.997 | 0.993-1.001 | .16 |
| Sex | Mare | 58 | 58 | Reference | | |
| | Stallion | 18 | 18 | 3.08 | 1.38-6.9 | .006 |
| | Gelding | 99 | 99 | 0.94 | 0.50-1.78 | .86 |
| Estimated AF duration | | 175 | 115 | 1.0012 | 1.00003-1.0024 | .04 |
| Previous unsuccessful cardioversion attempt | No | 156 | 156 | Reference | | |
| | Yes | 19 | 19 | 1.74 | 0.82-3.69 | .15 |
| RA dilation | No | 144 | 144 | Reference | | |
| | Yes | 31 | 31 | 1.65 | 0.86-3.15 | .13 |
| RV dilation | No | 148 | 148 | Reference | | |
| | Yes | 27 | 27 | 1.61 | 0.81-3.22 | .18 |
| MR | No | 92 | 92 | Reference | | |
| | Yes | 83 | 83 | 1.94 | 1.11-3.40 | .02 |
| MR grade | None | 92 | 92 | Reference | | |
| | Mild | 57 | 57 | 1.92 | 1.04-3.55 | .04 |
| | Moderate | 26 | 26 | 1.98 | 0.92-4.22 | .08 |
| TR | No | 97 | 97 | Reference | | |
| | Yes | 78 | 78 | 1.92 | 1.10-3.35 | .02 |
| TR grade | None | 97 | 97 | Reference | | |
| | Mild | 60 | 60 | 1.78 | 0.98-3.24 | .06 |
| | Moderate | 18 | 18 | 2.44 | 1.08-5.48 | .03 |
| Sotalol premedication | No | 144 | 144 | Reference | | |
| | Yes | 31 | 31 | 1.791 | 0.954-3.365 | .07 |
| IRAF | No | 170 | 170 | Reference | | |
| | Yes | 5 | 5 | 3.37 | 1.05-10.9 | .04 |
| Follow-up treatment with sotalol | No | 89 | 89 | Reference | | |
| | Yes | 86 | 86 | 1.51 | 0.87-2.63 | .14 |

Abbreviations: 95% CI, 95% confidence interval; AF, atrial fibrillation; HR, hazard ratio; IRAF, immediate recurrence of atrial fibrillation; LA, left atrium; MR, mitral regurgitation; N, number of horses; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation.

(HR 1.001, 95% CI 1.0001-1.0026, $P = .04$) were significant risk factors for recurrence. When analysis was performed on the last AF episode (179 cases), the multivariable model showed that IRAF (HR 4.41, 95% CI 1.27-15.3, $P = .02$), being a stallion (HR 3.59, 95% CI 1.48-8.7, $P = .005$), follow-up treatment with sotalol (HR 2.58, 95% CI 1.36-4.9, $P = .004$), presence of MR (HR 1.88, 95% CI 1.03-3.42, $P = .04$), and body weight (HR 0.995, 95% CI 0.990-0.9998, $P = .04$) were independent predictors of recurrence within 1 year.

The analysis performed on the data around the time of change of catheters showed that Type B catheters had a significantly lower cumulative amount of energy administered during TVEC ($P = .04$) and a significantly lower impedance (mean difference 8 Ω, 95% CI 1-14 Ω, $P = .02$). In cases in which there was need for ventricular pacing, a significantly higher cumulative amount of energy had been administered ($P < .001$). The R-AFCL and AF duration were not significantly correlated ($P = .09$) and no correlation could be found either between depth of catheter insertion and body weight or height at the withers (RA catheter depth—body weight: $P = .22$; PA catheter depth—body weight: $P = .12$; RA catheter depth—height at the withers: $P = .19$; PA catheter depth—height at the withers: $P = .25$).

## 4 | DISCUSSION

This retrospective case series of TVECs in a predominantly Warmblood study sample shows that a long R-AFCL and the absence of MR are associated with successful TVEC. Body weight, catheter type, the presence of TR and a previous AF episode were significantly correlated with the cumulative amount of energy administered until conversion. Independent risk factors for recurrence after a first AF episode were being a stallion, presence of MR, and a longer AF duration. When only the last AF episodes were included, being a stallion,

**TABLE 5** Variables included in the multivariable analysis for AF recurrence within 1 year, based on 179 horses (looking at their last AF episode)

| Variables | Level | N (including imputed values) | N (excluding missing data values) | HR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|
| Body weight | | 179 | 179 | 0.996 | 0.992-1.001 | .1 |
| Sex | Mare | 58 | 58 | Reference | | |
| | Stallion | 19 | 19 | 3.15 | 1.36-7.3 | .008 |
| | Gelding | 102 | 102 | 1.03 | 0.52-2.06 | .93 |
| Previous AF episode | No | 157 | 157 | Reference | | |
| | Yes | 22 | 22 | 1.68 | 0.78-3.60 | .18 |
| LA dilation | No | 140 | 140 | Reference | | |
| | Yes | 39 | 39 | 1.75 | 0.95-3.24 | .08 |
| RA dilation | No | 144 | 144 | Reference | | |
| | Yes | 35 | 35 | 1.96 | 1.05-3.67 | .04 |
| RV dilation | No | 150 | 150 | Reference | | |
| | Yes | 29 | 29 | 1.85 | 0.94-3.64 | .08 |
| MR | No | 96 | 96 | Reference | | |
| | Yes | 83 | 83 | 1.70 | 0.95-3.04 | .08 |
| MR grade | None | 96 | 96 | Reference | | |
| | Mild | 57 | 57 | 1.61 | 0.84-3.08 | .15 |
| | Moderate | 26 | 26 | 1.88 | 0.86-4.13 | .12 |
| Sotalol premedication | No | 148 | 148 | Reference | | |
| | Yes | 31 | 31 | 1.918 | 0.993-3.707 | .05 |
| IRAF | No | 174 | 174 | Reference | | |
| | Yes | 5 | 5 | 3.90 | 1.21-12.6 | .02 |
| Follow-up treatment with sotalol | No | 86 | 86 | Reference | | |
| | Yes | 93 | 93 | 2.35 | 1.25-4.40 | .008 |

Abbreviations: 95% CI, 95% confidence interval; AF, atrial fibrillation; HR, hazard ratio; IRAF, immediate recurrence of atrial fibrillation; LA, left atrium; MR, mitral regurgitation; N, number of horses; RA, right atrium; RV, right ventricle.

the presence of MR, body weight, IRAF during the TVEC procedure and follow-up treatment with sotalol revealed to be significant risk factors for recurrence.

The success rate of TVEC in our study sample was 94.4%, which is comparable with previously reported success rates.[18] Multiple horse and procedural characteristics have already been studied to predict success and ease of conversion for both pharmacological conversion with quinidine sulfate and TVEC. For quinidine sulfate, AF duration, presence of underlying cardiac disease, pretreatment with propafenone (with or without ACE-inhibitor) and plasma quinidine concentration impact treatment outcome.[1,4,17,31,32] For TVEC, some correlations have been described between energy requirement and body weight (sex-dependent: negative relation in females and positive relation in males) and a higher age has been shown to result in a higher energy requirement (only in females), however these findings were regarded as clinically irrelevant.[5,12] In our study sample, body weight was also significantly correlated with the cumulative amount of energy administered, albeit with a low odds ratio.

Underlying cardiac disease, with LA dilation as the most important factor, can decrease the likelihood of cardioversion, as it represents an ideal AF substrate.[1] For this reason, horses with severe echocardiographic abnormalities were excluded from this study, as treatment would not be advised in these cases due to decreased success rate and increased recurrence risk.[1,18] In this study, MR emerged as a determinant of TVEC success. This can be related to the fact that MR induces LA volume overload, increase of LA pressures and myocardial stretch, and therefore promotes AF stability.[33] Similarly, the presence of TR was related with a higher cumulative amount of energy and therefore a more difficult conversion. Also related to increased AF stability is our second determinant for success, the R-AFCL: the shorter the R-AFCL, the lower the chance for successful conversion. Atrial fibrillation itself induces shortening of the atrial effective refractory period, thus decreasing the chance that a reentry circuit encounters refractory tissue and consequently increasing AF stability.[27] As the AFCL is regarded as a measure for the atrial effective refractory period,[10,27] it can be stated that horses with a shorter R-AFCL will have more stable AF and will therefore be more difficult to convert. Likewise, a short R-AFCL has been associated with a higher cardioversion threshold in humans and dogs.[34-36]

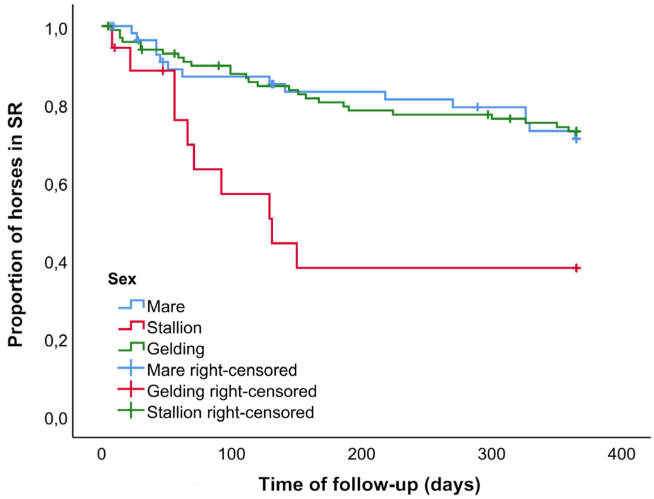


**FIGURE 2** Kaplan-Meier survival curves for horses grouped by sex (N = 175; 58 mares, 18 stallions, 99 geldings). Proportion of horses without AF recurrence after their first AF episode. Follow-up of 1 year. AF, atrial fibrillation

Catheter design and catheter positioning are identified as decisive factors for successful TVEC.[12,14] The shock catheters should be positioned in order to encompass as much atrial tissue as possible. Especially the positioning of the PA catheter has been stressed in past studies, showing that a dorsal and caudal position of the PA catheter in relation to the RA catheter should be pursued to maximize the chance for conversion and minimize energy requirement.[14,37] Catheter design has a major impact on shock delivery and therefore conversion efficiency. A large surface area coil reduces electrical resistance and consequently minimalizes focal peak current, allowing efficient shock delivery without damaging the cardiac tissue.[38-40] In our study, catheter Type B was significantly negatively correlated with cumulative energy levels during TVEC. To distinguish the influence of catheter type from gain of experience through time, specific analysis was performed on the data of the period around the change of catheters, and this proved indeed an increased cumulative amount of energy administered during TVEC when using the Type A catheters vs the Type B catheters. Moreover, the impedance was significantly higher when Type A catheters were used, suggesting an inherent difference in catheter properties between the 2 types. The Type A catheters are characterized by a shorter coil[14] and therefore a smaller surface area compared to the Type B catheters,[38] which might result in a higher resistance and therefore higher impedance at shock delivery while including less atrial tissue in the current flow.

A previous AF episode significantly predicted a higher cumulative amount of energy for conversion. A possible explanation is that horses with multiple recurrences probably have an ideal substrate for AF due to a combination of structural and electrical remodeling which results in a large number of reentry circuits and thus more stable AF. Shock delivery at low energy level might in those cases not be sufficient to interrupt enough reentry circuits to stop the arrhythmia. A previous AF episode has also been identified as a risk factor for recurrence in horses.[41]

The recurrence rate in this study was 31.9%, which is comparable with previous studies.[4,8,41,42] Risk factors for recurrence are mainly related to the basis of AF initiation: the need for a trigger and a substrate.[33] Underlying cardiac diseases, such as MR and atrial dilation, and advanced electrical and contractile remodeling, characterized by a shorter AFCL and a reduced atrial contractile function respectively, are known risk factors as they represent favorable substrate for AF initiation and perpetuation.[25,41,42] An increased burden of APDs after TVEC can provide the triggers for AF reinitiation and has been associated with a higher recurrence risk.[42] A long AF duration[4] implies the presence of major electrical,[21,43,44] contractile,[21,44] and structural remodeling[44] and an unsuccessful cardioversion attempt can indicate underlying myocardial disease or altered atrial electrophysiological properties.[41] Similarly to what has already been reported,[41,42] a low body weight and the presence of MR proved to be risk factors for recurrence in this study. A long estimated AF duration also revealed to be a risk factor for recurrence after a first AF episode, emphasizing the importance of prompt treatment of AF.[1]

Another significant predictor for recurrence in our study was the occurrence of IRAF, similarly to what has been shown in humans.[45] Immediately after cardioversion, the atrial tissue is a supervulnerable substrate for IRAF as the atrial effective refractory period and the conduction velocity are markedly decreased, widening the window of inducibility of AF by an APD.[46] IRAF is often initiated by a short-coupled APD,[47] and 3 of the 5 horses with IRAF in this analysis had a high burden of APDs and 1 even runs of AT on their 24-hour ECG 5 days after cardioversion, which might indicate the underlying presence of a firing focus increasing the risk for AF reinitiation.[45,48,49]

The choice of the authors to exclude the horses that experienced ERAF from the recurrence analysis was related to this increased sensitivity for induction of AF in an electrically remodeled atrium. Reverse electrical remodeling takes at least 3 to 7 days to be completed in humans,[28] dogs,[29] and goats,[27] and during this period the atria are extremely sensitive for reinitiation of AF by an APD, even in absence of profibrillatory factors such as atrial dilation or tissue fibrosis.[27] By excluding these cases, our study was focused on the risk factors for recurrence beyond incomplete electrical reverse remodeling.

Stallions experienced more recurrence in our study sample in comparison with mares and geldings. Estrogen is thought to be protective against atrial effective refractory period shortening after rapid atrial pacing in humans.[50] In addition, testosterone and estrogen have been suggested to play a role in the differences in ventricular repolarization pattern between men and women,[51] which would be related to different dispersion and density of calcium and potassium channels in the ventricular myocardium.[52,53] On the other hand, women experience recurrence after electrical cardioversion more often compared to men.[54] Another explanation could be found in differences in body conformation between males and females, as lean body mass has been identified as the predominant morphometric risk factor for AF in humans.[55] Stallions are known to have a higher fat-free mass than mares,[56] and in general castration increases body fat percentage.[57,58] In our study sample, no data were recorded on body conformation except body weight, therefore no conclusions can be drawn.

In 9/14 cases in our study, amiodarone administration during TVEC resulted in conversion when the normal shock procedure did not achieve sinus rhythm.[59] Amiodarone is a Vaughan-William class III antiarrhythmic drug and inhibits β-adrenoreceptors as well as potassium, sodium, and calcium channels. These effects prolong the AFCL, the repolarization phase and action potential duration. This reduces the number of reentry circuits that can coexist and therefore promotes AF termination.[60,61] In our study, catheters were repositioned during amiodarone administration in some horses which might have introduced bias. Further research is needed to assess if amiodarone can facilitate cardioversion in horses, as it does in humans.[62] Pretreatment with amiodarone to prevent IRAF has been reported in humans[63] and horses,[6] and was successful in 4 cases with repeated IRAF in our study, albeit using a different treatment regimen. Although no definite conclusions can be drawn based on our limited study sample, it might be advantageous to use amiodarone in challenging TVEC procedures.

Sotalol, a Vaughan-Williams class III-antiarrhythmic with β-blocking effects prolongs the atrial and ventricular effective refractory period[64] and AFCL[65] in horses and has therefore been suggested as possible oral antiarrhythmic in horses.[64] In this study, premedication with sotalol was randomly assigned in 44 cases and was univariably associated with a lower amount of cumulative energy until conversion, an effect that is also seen in humans.[66] However, in the multivariable analysis the importance of this variable was lost. In humans sotalol is also used to prevent AF recurrence, although other antiarrhythmic drugs, such as dronedarone, amiodarone, flecainide and propafenone, are preferred because of higher efficacy or improved safety profile.[3] Follow-up treatment with sotalol was positively associated with recurrence in our study. This can be explained by the fact that the majority of the horses in our sample received sotalol based on an estimated higher risk for recurrence. The set-up of our study was not designed to evaluate the efficacy of sotalol in prevention of AF recurrence as the treatments were not randomly assigned. Similarly to amiodarone, further research is needed to assess this effect.

Due to the retrospective nature of our study, some variables (eg, AF duration, R-AFCL) had considerable missing values, prompting the use of multiple imputation for analysis. Another limitation is that in 61.5% of the cases the horse received some kind of pharmacological treatment before, during or after TVEC, or a combination, which might have influenced TVEC outcome or recurrence. In addition, cumulative amount of energy administered during TVEC might have been high in some cases due to improper catheter position which was detected by echocardiography and resolved during the course of the TVEC procedure and therefore not related to catheter type or horse factors. Another limitation is that the exclusion of cases which were in the authors' view not eligible for treatment due to an increased recurrence risk but were treated nonetheless on the owner's request, was based on overall clinical, and therefore subjective, assessment of case history and echocardiographic findings in absence of guidelines that define clear cutoffs for treatment eligibility. A last limitation is that catheter depth was determined based on the length of the noninserted part of the catheter without radiographic control, therefore true depth of insertion was not determined. It should also be noted that the effect size of some significant predictors and risk factors, such as the R-AFCL (for TVEC success), body weight (for cumulative amount of energy and recurrence) and estimated AF duration (for recurrence), was small and that therefore the clinical relevance of these variables should be interpreted with caution.

Transvenous electrical cardioversion remains an effective first-choice treatment option for atrial fibrillation in horses. This study emphasizes that horse-related factors remain the primary determinants of cardioversion success and difficulty, next to design of the shock catheters. Prompt treatment should be encouraged in order to avoid advanced atrial remodeling, and together with previously reported risk factors, sex, IRAF and AF duration should be taken into account when determining the prognosis after TVEC.

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## CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

## HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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